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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JIANG, DONG	
ART UNIT	PAPER NUMBER
1646	5

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,532	KEITH ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *6 and 7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 8-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-13* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED OFFICE ACTION

Applicant's election of species of "gastroesophageal reflux disease" in Paper No. 4 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's preliminary amendment in paper No. 4, filed on 19 December 2002 is acknowledged and entered. Following the amendment, claims 10-13 are amended.

Currently, claims 1-13 are pending, and claims 1-5 and 8-13 are under consideration. Claims 6 and 7 are withdrawn from further consideration as being drawn to a non-elected species.

The references listed on the PTO-1449 in paper No. 2 are not present in the current application file. In response to this Office Action only, applicants may submit another set of the same references, and the Examiner will consider them as though they were submitted with IDS in paper No. 2.

Double Patenting Rejections:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1, 2, and 11-13 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 6 of U.S. Patent No. 6,126,933.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1 and 6 of the U.S. patent '933 are directed to a method of treating an inflammatory bowel disease by administering IL-11 at a dosage range of 1-250 ug/kg body weight. As the inflammatory bowel disease is a type of gastrointestinal motility disorder, it renders the genus of "gastrointestinal motility disorder" obvious because the species would anticipate the genus.

With respect to claims 11-13, although claim 1 of the patent does not mention the effect of the increased plasma or tissue concentration of motilin (as claims 11 and 12), or improved contractile parameters of gut wall (as claim 13) by IL-11 administration, as the therapeutic ingredient and the method steps are the same between the patent and the instant application, the same effect would be inherent. It is, therefore, obvious that they are not patentably distinct from each other.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, and 11-13 are also rejected under 35 U.S.C. 103(a) as being obvious over claim 1 of U.S. Patent No. US 6,126,933 for the same reasons addressed above.

The applied reference, US 6,126,933, has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing

under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 8-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a method for treating certain gastrointestinal motility disorders associated with inflammatory response, such as colitis, does not reasonably provide enablement for claims to a method for treating or *preventing* any or all gastrointestinal motility disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 1-5 and 8-13 are directed to a method for treating or preventing a gastrointestinal motility, such as gastroesophageal reflux disease, by administering interleukin-11. The specification discloses two working examples to support the invention. The basis of the invention seems to be laid upon the experimental observation that IL-11 treatment during colitis markedly increased plasma motilin levels in rabbits with TNBS-induced colitis (Example 2, page 11, lines 22-24). The applicant, therefore, extrapolates that IL-11 can be used in treating or preventing gastrointestinal motility disorders such as gastroesophageal reflux disease, post-operative adynamic ileus, or intolerance to oral feeding in preterm infants claims 5-7 and 10), as it is indicated in the prior art that increasing plasma concentration of motilin or its agonists is beneficial to gastroesophageal reflux disease (A. Pennathur et al., Am J Surg., 1994, 167(1): 169-173), post-operative adynamic ileus (T. Yokoyama et al., Neurogastroenterol Motil., 1995, 7(4): 199-210) and intolerance to oral feeding in preterm infants (C.L. Berseth, Clin Perinatol., 1996, 23(2): 179-90) although some controversy and uncertainty still exist (A.J. Smith et al., Dis Colon Rectum, 2000, 43(3): 333-337; E. Ng et al., Cochrane Database Syst Rev, 2000, (2): CD001815). Additionally, claim 1-4, 8-9, given the broadest breadth, reads on treating or preventing any or all gastrointestinal motility disorders. It is noticed, however, that the animal model, TNBS-induced colitis in rabbits, used in the working examples of the current invention is primarily suitable for studying in treatment of inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. IL-11 has been shown in such inflammatory bowel disease model to have anti-inflammatory effects and protective effect on intestinal mucosa. However, such model is not typically acceptable for studying gastrointestinal motility disorders in general. A search of the prior art demonstrates accepted models related to studying gastrointestinal motility disorders. For instance, De Winter et al. created a rat model of post-operative ileus by laparotomy (Gut, 1999, 45(5): 713-8); and Inatomi et al. monitored gastrointestinal contractions in normal dogs after stimulation with motilin analog, EM-523 (J Pharmacol Exp Ther, 1989, 251(2): 707-12). The examiner find that the evidence to support the current invention is less persuasive because the involvement of multiple pathologic factors specific in colitis may contribute to the changes observed, which are not representative of most gastrointestinal motility disorders. For instance, TNBS-induced colitis causes extensive damage in the structure of the colon, and has specific

effect on receptor-medicated pathways (I. Depportere et al., Am J Physiol., 1999, 277(1 Pt 1): G61-8). Additionally, Zlatkina et al. (TERAPEVTICHESKII ARKHIV, 1994, 66(12): 67-70) has shown that a high concentration of blood motilin is observed in ulcerative colitis patients, and Besterman et al. has shown that plasma motilin levels are increased during gastrointestinal inflammation (Scand. J Gastroenterol, 1983, 18:845-52). It is, therefore, reasonable to question about a possible coincidence (i.e. what the cause of the increase in motilin is) in the instant case when motilin level increases following the treatment of IL-11, especially as the applicant did not provide clear control data to support the conclusion. Further, there is no common pathology among disorders such as inflammatory colitis, gastroesophageal reflux disease, and post-operative adynamic ileus. As such, a working example of colitis cannot be used to support a method of treating any or all gastrointestinal motility disorders. Additionally, the applicant stated that "plasma motilin levels were not influenced by the inflammatory process (649±69 vs. 724±126 pg/ml, page 11, line 1)", which clearly disagree with the data from IL-11 treated group. This "base" level of plasma motilin is much higher or comparable than the values (199±77 or 799±201) from IL-11 treated group, with 4 or 40 ug/kg per day (see page 11, line 14).

More recently, a similar study by the applicant using the same animal model (Depoortere et al., J. Pharmacol Exp Ther, 2000, 294(3): 983-90), has indicated that "inflammation per se decreased motilin receptor density and maximal active tension by 71% and 58% respectively" in the rabbits with TNBS-induced colitis, IL-11 treatment restored motilin receptor density, and there is a clear correlation in changes between maximal active tension and motilin receptor density (Figure 9). It is obvious that the mechanism of gastrointestinal motility disorder indicated in this study is not applicable to all gastrointestinal motility disorders because it seems that the loss of the receptor, rather than the ligand (motilin) in the colitis model, plays a important role in affecting the motility. It is, therefore, not proper to extrapolate that IL-11 can be used in treating any or all gastrointestinal motility disorders based on the animal model provided in the instant case.

Given the reasons above, the skilled artisan would not reasonably expect that the claimed methods could be practiced to advantage to treat or prevent any or all gastrointestinal motility disorders except those caused by gastrointestinal inflammation as IL-11 is well known in the art for its anti-inflammatory effect and protective effect on gastrointestinal mucosa. Additionally,

the applicant did not provide enough guidance in the disclosure as to no proper control data are presented, and no instruction is given on how many animals to be used in each group, and how and what "contractile parameters" (in vivo or in vitro) to be measured. Further the experimental model is not representative for studying gastrointestinal motility disorders, and there is no common pathology between inflammatory colitis and other gastrointestinal disorders such as gastroesophageal reflux disease. Given the broad breath of claims 1-4 and 8-9, which encompasses treating or preventing any or all gastrointestinal motility disorders, in light of the predictability of the art, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require extensive undue experimentation for the skilled artisan to practice the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11-13 are indefinite because there is no direct correlation between "increasing the plasma concentration" or "increasing the tissue concentration" or "improving the contractile parameters" and "therapeutically effective amount" which could be different from the amount enough to cause increasing the plasma or tissue concentration, or improving the contractile parameters. Omission of "therapeutically" would be remedial.

Claim 11 is further indefinite because it is unclear what "the *plasma* concentration of motilin *in the duodenal mucosa*" is meant.

Claim 13 is further indefinite because it is not clear what a "contractile parameter" is. There is no limiting definition of the term "contractile parameters" in the specification. The metes and bounds of the "contractile parameters" in the claims are vague due to the difference between "in vitro" contractile parameters and "in vivo" contractile parameters.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Du et al. (Blood, 1994, 83:33-37).

Du et al. disclose a method of treating small intestinal mucositis in a mouse model with IL-11, which anticipates claim 1 in the instant case. The method steps and IL-11 dosage (250 ug/kg/day) used in Du's experiments were in the range of the claims 2-4. Additionally, claims 11-13 are anticipated by the reference because the recited increased plasma or tissue concentration of motilin or improved contractile parameters are inherent features of IL-11 treatment and would therefore necessarily have occurred.

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 703-305-1345. The examiner can normally be reached on Monday - Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

LORRAINE SPECTOR
PRIMARY EXAMINER

Dong Jiang, Ph.D.
Patent Examiner
AU1646
3/18/03